Amendment to the Specification

1. Please insert at page 1, after the title, the following paragraph:

-- Statement of Government Support

This invention was made in part by grant number DA 11946 from the National Institute on Drug Abuse. The U.S. Government therefore has certain rights in the invention. --

2. Please replace the paragraph bridging pages 68 and 69 with the following amended paragraph:

-- Rats (n=9) were trained to respond according to a modification of the discrete-trial current-threshold procedure of Kornetsky and Esposito (1979). Briefly, a trial was initiated by the delivery of a non-contingent electrical stimulus. This electrical reinforcer had a train duration of 500 ms and consisted of 0.1 msec rectangular cathodal pulses that were delivered at a frequency of 50-100 Hz. The frequency of the stimulation was selected for individual animals so that baseline current-intensity thresholds of each subject were within 50-200 ⊟μA, and thus allowed both threshold elevations and lowerings to be detected. The frequency was held constant throughout the experiment. A one-quarter turn of the wheel manipulandum within 7.5 sec of the delivery of the non-contingent electrical stimulation resulted in the delivery of an electrical stimulus identical in all parameters to the non-contingent stimulus that initiated the trial. After a variable inter-trial interval (7.5-12.5 sec, average of 10 sec), another trial was initiated with the delivery of a non-contingent electrical stimulus. Failure to respond to the non-contingent stimulus within 7.5 sec resulted in the onset of the inter-trial interval. Responding during the inter-trial interval delayed the onset of the next trial by 12.5 sec. Current levels were varied in alternating descending and ascending series. A set of

three trials was presented for each current intensity. Current intensities were altered in 5 μA steps. In each testing session, four alternating descending-ascending series were presented. The threshold for each series was defined as the midpoint between two consecutive current intensities that yielded "positive scores" (animals responded for at least two of the three trials) and two consecutive current intensities that yielded "negative scores" (animals did not respond for two or more of the three trials). The overall threshold of the session was defined as the mean of the thresholds for the four individual series. Each testing session was .about.30 min in duration. The time between the onset of the non-contingent stimulus and a positive response was recorded as the response latency. The response latency for each test session was defined as the mean response latency of all trials during which a positive response occurred. After establishment of stable ICSS reward thresholds, rats were tested in the ICSS procedure once daily except for the time-course of cocaine's lowering actions on ICSS thresholds when rats were tested at time-points according to the experimental design.
–

3. Please replace the paragraph bridging pages 81 and 82 with the following amended paragraph:

-- Reduced serotonergic neurotransmission has been implicated in the etiology of non-drug induced depression. Evidence in favor of this hypothesis includes demonstrations of the efficacy of serotonergic antidepressant treatments, reduced cerebrospinal fluid levels of serotonin metabolites, endocrine measures reflecting reduced serotonergic neurotransmission and the exacerbation of depressive symptomatology seen after serotonin depletion in depressed patients (for reviews, Caldecott-Hazard et al. 1991; Markou et al. 1998). Recent advances in the treatment of depression indicate that the co-administration of pindolol accelerates the delayed onset of the antidepressant action of selective serotonin reuptake inhibitors (SSRIs) (Rickels

et al. 1989; Blier and de Montigny, 1999; Bordet et al. 1998; Zanardi et al. 1998; McAskill et al. 1998). It has been hypothesized that the acceleration of the antidepressant action of SSRIs may be through the 5-HT_{1A} receptor antagonist action of pindolol, although this drug has widespread effects through antagonist actions at 5-HT_{1A}, 5-HT_{1E}, and ⊟β-adrenergic receptors (Assie and Koek 1996; Bourin et al. 1998; Gobert and Millan 1999) and partial agonist actions at ⊟β-adrenergic receptors (Clifford et al. 1998; Gobert and Millan 1999; Pauwels and Palmier 1994). In vivo microdialysis work demonstrated that the acute co-administration of a 5-HT_{1A} receptor antagonist together with an SSRI rapidly elevated forebrain serotonin dialysate levels beyond levels seen after acute SSRI treatment alone (Auerbach and Hjorth 1995; Hjorth 1993; Kreiss and Lucki 1995; Artigas et al 1996; Blier and de Montigny 1994; however, see Cremers et al. 2000). --

4. Please replace the paragraph bridging pages 84 and 85 with the following amended paragraph:

-- At the start of each trial rats received a non-contingent electrical stimulus. During the following 7.5 sec, the limited hold, if the subjects responded by turning the wheel manipulandum a quarter turn (positive response) they received a second, contingent stimulus identical to the previous non-contingent stimulus. During a 2 sec period immediately following a positive response, further responses were recorded as extra responses but had no consequence. If no response occurred during the 7.5 sec limited hold period a negative response was recorded. The inter-trial interval (ITI), which followed the limited hold period, had an average duration of 10 sec (ranging from 7.5-12.5 sec). Responses that occurred during the ITI were recorded as time-out responses and resulted in a further 12.5 sec delay of the onset of the next trial.

Stimulation intensities were varied according to the classical psychophysical method of limits. The subjects received four alternating series of ascending and descending current intensities starting with a descending series. Within each series the stimulus intensity was altered by 5 ±µA steps between each set of trials (three trials per set). After training in the above procedure, rats were tested until stable baseline thresholds had been achieved L+10% over a 5-day period). Drug testing commenced only after performance had stabilized, which typically occurred after two to three weeks of daily baseline testing. Each test session typically lasted 30 minutes and provided two dependent variables for behavioral assessment: --

5. Please replace the paragraph bridging pages 94 and 95 with the following amended paragraph:

-- The rapid restoration of the sensitivity to the electrical stimulation observed following the co-administration of either paroxetine or fluoxetine and a 5-HT_{1B} receptor antagonist may be attributable to increased serotonergic transmisson in forebrain structures such as the frontal cortex, hippocampus and the striatum (Bel and Artigas 1993: Dreshfield et al. 1996; 1997; Invernizzi et al. 1994; Gobert and Millan 1999). These data are consistent with the hypothesis that the rapid onset of action of the clinical antidepressant action of SSRIs when combined with pindolol (Bordet et al 1998; Tome et al 1997a; 1997b; Zanardi et al 1998; however, see Berman et al 1999) is partly attributable to pindolol's 5-HT_{1A} receptor antagonist properties. However, other receptors such as 5-HT_{1B} and ±β-adrenergic receptors may also contribute to pindolol's augmentation of SSRI antidepressant effects (see Introduction). --